AMINE BISULFITES, AND THEIR USE AS RESOLVING AGENTS

BY

JOHN DOUGLAS GARBER

B.S., The Pennsylvania State College, 1940

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1943

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INTRODUCTION

Because of the basic properties of amines it is at least theoretically possible to form an amine bisulfite, which might be expected to add to the carbonyl double bond in the same manner as sodium bisulfite. Unfortunately, early workers[1,2] could not agree on the correct empirical formulas for the products obtained from the reaction of amine-sulfur dioxide complexes with carbonyl compounds. Even though the reaction was carried out under anhydrous conditions the products were referred to as "sulfites" and "bisulfites".

This investigation was begun in an attempt to clarify the course of certain of the reactions of amines with sulfur dioxide, and to study the properties and reactions of the products formed, with particular emphasis on the addition of amine bisulfites to carbonyl compounds. When this latter reaction was found to be quite general, it was thought that the resolution of a racemic carbonyl compound could be effected by the use of an optically active amine bisulfite. Fractional cyrstallization of the resulting diastereoisomers might result in the isolation of an optically pure fraction which could be decomposed to the optically active carbonyl compound.

EXPERIMENTAL AND DISCUSSION OF RESULTS

When sulfur dioxide was passed into an equimolar mixture of water and an aliphatic amine, a white precipitate was formed. This product, chiefly the amine sulfite, was not isolated but the introduction of sulfur dioxide was continued until a homogeneous, yellow, viscous liquid was produced. Addition of an excess of a suitable carbonyl compound caused a vigorous reaction to occur, accompanied by an immediate decolorization of the bisulfite solution and evolution of heat. Soon the reaction mixture solidified to produce a substantially theoretical yield of the amine bisulfite addition compound.

Bisulfites were formed from benzylamine, α-phenylethylamine, β-phenylethylamine, *sec*-butylamine and β-naphthol phenylaminomethane. Each of these bisulfites was allowed to react with the following carbonyl compounds: acetone, cyclopentanone, cyclohexanone, 3-methylcyclohexanone, benzaldehyde, heptaldehyde, isovaleraldehyde and valeraldehyde. The amine bisulfite addition compounds that resulted were crystallized from ethanol and analyzed for sulfur by a method that was developed especially for this type of substance. The sample was decomposed with aqueous alkali, and the solution was poured into water containing a slight excess of acid and a ten per cent excess of standard iodine. Back-titration with standard sodium thiosulfate followed immediately.

Even though the melting points of almost all of the amine bisulfite addition compounds studied fell in the narrow temperature range of 100-130°, other properties of this type of substance warrant further investigation as to its desirability as a derivative of carbonyl compounds.

It was postulated that the yellow color of the original amine bisulfite solution was due to a complex, perhaps of the type $(RNH_2)_x:(SO_2)_y$. Such a complex, in the presence of water and a suitable carbonyl compound, could react to form an amine bisulfite addition compound. The evolution of sulfur dioxide in the latter reaction can be cited as one piece of evidence that y must be greater than x. Moreover, Bright and Jasper[3] have shown that the 1:1 trimethylamine-sulphur dioxide complex is colorless.

In order that a reaction might occur between a carbonyl compound and either a thionylamine or the anhydrous amine-sulfur dioxide complex, the presence of water was found to be essential. In each case the sole product isolated was the corresponding amine bisulfite addition compound.

An attempt was made to add benzylamine sulfite to coumarin. A product was isolated whose structure could not be determined; however, it was shown that the compound was not analogous to the sodium sulfite addition product obtained by Dey and Row.[4] It has been shown[5] that

sodium bisulfite will add to the carbon-carbon double bond in cyclohexene. Only the amine sulfate was isolated from the reaction mixture when benzylamine sulfite was caused to react with cyclohexene or allyl alcohol.

When the bisulfite addition compound of *d*-α-phenylethylamine and *dl*-3-methylcyclohexanone was crystallized four times from ethanol an optically pure fraction was obtained in 29 per cent yield, m. p. 126-127°; $[\alpha]_D^{26}=+1.4°$. This salt was decomposed and the ketone converted to a semicarbazone, $[\alpha]_D^{20}=-21.0°$. Adams, Smith and Loewe[6] previously reported a value of —20.7° for the *d*-3-methylcyclohexanone derivative. After the *l*-α-phenylethylamine bisulfite addition compound of the *dl*- ketone was treated in a similar manner, the semicarbazone of *l*-3-methylcyclohexanone was isolated, $[\alpha]_D^{20}=+20.8°$. *l*-Menthylamine and *d*-β-naphthol phenylaminomethane bisulfites were employed with indifferent success in an attempted resolution of the racemic ketone.

p-sec-Butylbenzaldehyde was prepared in yields of 66 per cent from N-methylformanilide and the aryl lithium compound that resulted from the action of lithium on *p*-iodo-*sec*-butylbenzene.[7] The *d*-α-phenylethylamine bisulfite addition compound was formed from the *dl*- aldehyde. When the procedure described above was employed a semicarbazone was isolated, m.p. 208-208.5°; $[\alpha]_D^{28}=-2.3°$. The rotation of the pure ketone, which was obtained from the same fraction as the active semicarbazone, indicated that probably only partial resolution had been realized, $[\alpha]_D^{33}=-0.19°$; b. p. 115-116° (13 mm.); $n_D^{25}=1.5247$. *l*-Menthylamine bisulfite was used unsuccessfully in an attempt to resolve *dl-p-sec*-butylbenzaldehyde, and *d*-β-naphthol phenylaminomethane bisulfite reacted abnormally to form a Schiff base instead of the desired addition compound.

One recrystallization of the crude product that resulted from the action of *d*-α-phenylethylamine bisulfite on *dl*-β-methylhydrocinnamaldehyde gave a fraction whose specific rotation was —20.7°. The enantiomorph of this addition compound was obtained by use of the *l*- amine bisulfite, $[\alpha]_D^{32}=+21.3°$.

These two fraction were decomposed and the aldehyde converted to a 2,4-dinitrophenylhydrazone, which was optically active in each case.

An improved synthesis for *dl*-β-methylhydrocinnamaldehyde[8] was developed. β-Bromoisopropylbenzene was prepared in 60 per cent yields by the action of allyl bromide on benzene in the presence of sulfuric acid. When the Grignard reagent was formed and allowed to react with N-methylformanilide, there was isolated 50 per cent of the theoretical amount of β-methylhydrocinnamaldehyde.

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Vita

The writer was born on May 12, 1920, in Minneapolis, Minnesota. He received his elementary schooling in Morgantown, West Virginia, and graduated from Morgantown High School in 1936. He received the degree of Bachelor of Science in the Chemistry Curriculum from the Pennsylvania State College in June, 1940, and the following September entered the Graduate School of the University of Illinois. There he was a teaching assistant for two years and held a University Fellowship for the next three semesters.

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